

C 18 101. (Amended) The attenuated tumor targeted bacteria of claim 13, wherein the antisense molecule is double-stranded or single-stranded DNA, double-stranded or single-stranded RNA, or a triplex molecule.

102. (Amended) The attenuated tumor targeted bacteria of claim 13, wherein the anti-tumor protein is a ribosome inactivating protein.

C 19 104. (Amended) The attenuated tumor targeted bacteria of claim 13, wherein the pro-drug converting enzyme is cytochrome p450 NADPH oxidoreductase.

C 20 113. (Amended) The pharmaceutical composition of claim 26, wherein at least one of the secondary effector molecules is a release factor.

C 21 126. (Amended) The method of claim 49, wherein at least one of the secondary effector molecules is a release factor.

C 22 139. (Amended) The attenuated tumor targeted bacteria of claim 13, wherein the pro-drug converting enzyme is cytosine deaminase.

REMARKS

At the outset, Applicants acknowledge the Office Action, mailed November 19, 2002, which states that the Response to Restriction Requirement Under 37 C.F.R. § 1.142 and Amendment Under 37 C.F.R. § 1.143, filed August 22, 2002, ("Reponse") has been entered into the record of the present application. Applicants note that the Office Action incorrectly states that claims 2-14, 16, 26-38, 40, 49-63, 72, 86, 94 and 100-141 are pending in this application. Claim 62 was cancelled in the Response. Therefore, upon entry of the Response, claims 2-14, 16, 26-28, 40, 49-61, 63, 72, 86, 94 and 100-141 are pending in this application.

Applicants also acknowledge the Office Communication, mailed December 19, 2002, which states that the Preliminary Amendment Under 37 C.F.R. § 1.115, filed November 8, 2002, ("Preliminary Amendment") has not been entered into the record of the present application because entry of the Preliminary Amendment might require a new Office Action. The Office Communication requires that Applicants respond to the Office Action, mailed November 19, 2002, and gives Applicants the option of resubmitting the Preliminary Amendment along with the response to the Office Action. Accordingly, Applicants herein respond to the Office Action, mailed November 19, 2002, and resubmit

the claim amendments set forth in the Preliminary Amendment filed on November 8, 2002, with some changes to reflect the response to the Office Action.

The Office Action, mailed November 19, 2002, requires an election under 35 U.S.C. § 121 to one of the following inventions:

Group I: Claims 2, 3-14, 16, 26-38, 40, 49-61, 63 and 100-141, drawn to an attenuated tumor targeting bacteria, a pharmaceutical composition comprising the bacteria and a method of delivering an effector molecule to a tumor, classified in class 435, subclass 93.2.

Group II: Claims 72-86 and 94, drawn to a method of treating a tumor using a combination of a chemotherapeutic composition and an attenuated tumor targeting bacteria, classified in class 435, subclass 93.2.

The Office Action also requires under 35 U.S.C. § 121 that Applicants elect a single species from each of the following genres:

- I. A primary effector molecule from the following: TNF-alpha, an anti-angiogenic factor, a tumor inhibitory enzyme, a cytotoxic peptide, bacteriocin family, hemolysin, CNF-1, CNF-2 and PMT;
- II. A primary effector molecule derived from one of the following: an animal, a plant, a bacterium, and a virus; and
- III. A secondary effector molecule from one of the following: an antisense molecule, a ribozyme, an antigen, an anti-tumor protein, a pro-drug converting enzyme, an immunomodulatory agent, a bacteriocin release factor, an inhibitor of oxide synthase, an inhibitor of endothelial nitric oxide and a release factor.

In response to the restriction requirement, Applicants, through their undersigned representatives, hereby elect to prosecute the subject matter of Group I (claims 2, 3-14, 16, 26-38, 40, 49-61, 63 and 100-141), drawn to an attenuated tumor targeting bacteria, a pharmaceutical composition comprising the bacteria and a method of delivering an effector molecule to a tumor. Applicants have canceled claims 72-86 and 94, drawn to the non-elected group, without prejudice to Applicants' right to prosecute the subject matter of the canceled claims in related applications. Further, in response to the species election requirement, Applicants, through their undersigned representatives, hereby elect the following species: an anti-angiogenic factor as the primary effector molecule; an animal as

the organism from which the primary effector molecule is derived; and a bacteriocin release factor as the secondary effector molecule. Applicants confirm their election of endostatin as the species of the anti-angiogenic factor made in the Response To Restriction Requirement Under 37 C.F.R. § 1.142 and Amendment Under 37 C.F.R. § 1.143, filed August 22, 2002.

Applicants have amended claims 3, 5, 7, 9, 11-14, 16, 27, 29, 31, 33, 35-38, 40, 50, 52, 54, 56, 58-61, 63, 101, 102, 104, 113, 126, and 139 to correct the dependencies of the claims in view of the cancellation of claims. A marked-up version of the amended claims, with deletions and additions indicated by brackets and underlining respectively, is attached hereto as Exhibit A. Applicants respectfully assert that the claim amendments do not constitute new matter. Therefore, upon entry of the present Amendment, claims 2-14, 16, 26-38, 40, 49-61, 63 and 100-141 will be pending in the present application. For the Examiner's convenience, a copy of the claims that will be pending upon entry of this Amendment is attached hereto as Exhibit B.

Applicants respectfully request entry of the amendments and remarks made herein into the file history of the present application.

Date February 5, 2003

Respectfully submitted,

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EXHIBIT A

MARKED-UP VERSION CLAIMS AMENDED ON FEBRUARY 5, 2003

IN U.S. PATENT APPLICATION SERIAL NO. 09/645,415

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3. (Amended) The attenuated tumor-targeted bacteria of claim [1 or] 2, wherein at least one of the primary effector molecules is a TNF family member.

5. (Amended) The attenuated tumor-targeted bacteria of claim [1 or] 2, wherein at least one of the primary effector molecules is an anti-angiogenic factor.

7. (Amended) The attenuated tumor-targeted bacteria of claim [1 or] 2, wherein at least one of the primary effector molecules is a bacteriocin family member with the proviso said bacteriocin is not BRP.

9. (Amended) The attenuated tumor targeted bacteria of claim [1 or] 2, wherein at least one of the primary effector molecules is a tumor inhibitory enzyme.

11. (Amended) The attenuated tumor targeted bacteria of claim [1 or] 2, wherein at least one of the primary effector molecules is hemolysin, verotoxin, CNF1, CNF2, or PMT.

12. (Amended) The attenuated tumor-targeted bacteria of claim [1 or] 2, wherein at least one of the primary effector molecules is derived from an animal, plant, bacteria, or virus.

14. (Amended) The attenuated tumor-targeted bacteria of claim [1 or] 2, wherein the attenuated tumor-targeted bacteria is *Salmonella*.

16. (Amended) The attenuated tumor-targeted bacteria of claim 2, wherein at least one of the secondary effector molecules is a bacteriocin release factor (BRP).

27. (Amended) The pharmaceutical composition of claim [25 or] 26, wherein at least one of the primary effector molecules is a TNF family member.

29. (Amended) The pharmaceutical composition of claim [25 or] 26, wherein at least one of the primary effector molecules is an anti-angiogenic factor.

31. (Amended) The pharmaceutical composition of claim [25 or] 26, wherein at least one of the primary effector molecules is a bacteriocin family member with the proviso said bacteriocin is not BRP.

33. (Amended) The pharmaceutical composition of claim [25 or] 26, wherein at least one of the primary effector molecules is a tumor inhibitory enzyme.

35. (Amended) The pharmaceutical composition of claim [25 or] 26, wherein at least one of the primary effector molecules is hemolysin, verotoxin, CNF1, CNF2, or PMT.

36. (Amended) The pharmaceutical composition of claim [25 or] 26, wherein at least one of the primary effector molecules is derived from an animal, plant, bacteria, or virus.

37. (Amended) The pharmaceutical composition of claim 26, wherein at least one of the secondary effector molecules is an immunomodulating agent, an anti-tumor protein, a pro-drug converting enzyme, an antisense molecule, a ribozyme, or an antigen.

38. (Amended) The pharmaceutical composition of claim [25 or] 26, wherein the attenuated tumor-targeted bacteria is *Salmonella*.

40. (Amended) The pharmaceutical composition of claim 26, wherein at least one of the secondary effector molecules is a bacteriocin release factor (BRP).

50. (Amended) The method of claim [48 or] 49, wherein at least one of the primary effector molecules is a TNF family member.

52. (Amended) The method of claim [48 or] 49, wherein at least one of the primary effector molecules is an anti-angiogenic factor.

54. (Amended) The method of claim [48 or] 49, wherein at least one of the primary effector molecules is a bacteriocin family member with the proviso said bacteriocin is not BRP.

56. (Amended) The method of claim [48 or] 49, wherein at least one of the primary effector molecules is a tumor inhibitory enzyme.

58. (Amended) The method of claim [48 or] 49, wherein at least one of the primary effector molecules is hemolysin, verotoxin, CNF1, CNF2 or PMT.

59. (Amended) The method of claim [48 or] 49, wherein at least one of the primary effector molecules are derived from an animal, plant, bacteria, or virus.

60. (Twice Amended) The method of claim 49, wherein at least one of the secondary effector molecules is an anti-tumor protein, an immunomodulating agent, a pro-drug converting enzyme, an antisense molecule, a ribozyme, or an antigen.

61. (Amended) The method of claim [48 or] 49, wherein the attenuated tumor-targeted bacteria is *Salmonella*.

101. (Amended) The attenuated tumor targeted bacteria of claim [2] 13, wherein the antisense molecule is double-stranded or single-stranded DNA, double-stranded or single-stranded RNA, or a triplex molecule.

102. (Amended) The attenuated tumor targeted bacteria of claim [2] 13, wherein the anti-tumor protein is a ribosome inactivating protein.

104. (Amended) The attenuated tumor targeted bacteria of claim [2] 13, wherein the pro-drug converting enzyme is cytochrome p450 NADPH oxidoreductase.

113. (Amended) The pharmaceutical composition of claim 26, wherein at least one of the secondary effector molecules is a release factor.

126. (Amended) The method of claim 49, wherein at least one of the secondary effector molecules is a release factor.

139. (Amended) The attenuated tumor targeted bacteria of claim [2] 13, wherein the pro-drug converting enzyme is cytosine deaminase.